

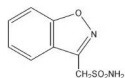
## ZONISAMIDE - zonisamide capsule

Mylan Pharmaceuticals Inc.

### DESCRIPTION

Zonisamide is an antiseizure drug chemically classified as a sulfonamide and unrelated to other antiseizure agents. The active ingredient is zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The molecular formula is  $C_8H_8N_2O_3S$  with a molecular weight of 212.23. Zonisamide is a white or almost white crystalline powder,  $pK_a = 10.2$ , and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL).

The chemical structure is:



Zonisamide is supplied for oral administration as capsules containing 25 mg, 50 mg or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The empty gelatin capsule shells contain D&C Red No. 28, FD&C Blue No. 1, gelatin and titanium dioxide. In addition, the 100 mg empty gelatin capsule contains FD&C Red No. 3.

The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

The precise mechanism(s) by which zonisamide exerts its antiseizure effect is unknown. Zonisamide demonstrated anticonvulsant activity in several experimental models. In animals, zonisamide was effective against tonic extension seizures induced by maximal electroshock but ineffective against clonic seizures induced by subcutaneous pentylenetetrazol. Zonisamide raised the threshold for generalized seizures in the kindled rat model and reduced the duration of cortical focal seizures induced by electrical stimulation of the visual cortex in cats. Furthermore, zonisamide suppressed both interictal spikes and the secondarily generalized seizures produced by cortical application of tungstic acid gel in rats or by cortical freezing in cats. The relevance of these models to human epilepsy is unknown.

Zonisamide may produce these effects through action at sodium and calcium channels. *In vitro* pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type  $Ca^{2+}$  currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. *In vitro* binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other *in vitro* studies have demonstrated that zonisamide (10 to 30 mg/mL) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse spinal cord neurons) or neuronal or glial uptake of [ $^3H$ ]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. *In vivo* microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide.

#### Pharmacokinetics

Following a 200 mg to 400 mg oral zonisamide dose, peak plasma concentrations (range: 2 to 5 mcg/mL) in normal volunteers occur within 2 to 6 hours. In the presence of food, the time to maximum concentration is delayed, occurring at 4 to 6 hours, but food has no effect on the bioavailability of zonisamide. Zonisamide extensively binds to erythrocytes, resulting in an 8-fold higher concentration of zonisamide in red blood cells (RBC) than in plasma. The pharmacokinetics of zonisamide are dose proportional in the range of 200 mg to 400 mg, but the  $C_{max}$  and AUC increase disproportionately at 800 mg, perhaps due to saturable binding of zonisamide to RBC. Once a stable dose is reached, steady state is achieved within 14 days. The elimination half-life of zonisamide in plasma is about 63 hours. The elimination half-life of zonisamide in RBC is approximately 105 hours.

The apparent volume of distribution (V/F) of zonisamide is about 1.45 L/kg following a 400 mg oral dose. Zonisamide, at concentrations of 1 to 7 mcg/mL, is approximately 40% bound to human plasma proteins. Protein binding of zonisamide is unaffected in the presence of therapeutic concentrations of phenytoin, phenobarbital or carbamazepine.

#### Metabolism and Excretion

Following oral administration of  $^{14}C$ -zonisamide to health volunteers, only zonisamide was detected in plasma. Zonisamide is excreted primarily in urine as parent drug and as the glucuronide of a metabolite. Following multiple dosing, 62% of the  $^{14}C$  dose was recovered in the urine, with 3% in the feces by day 10. Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4 (CYP3A4). Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately 0.30 to

0.35 mL/min/kg in patients not receiving enzyme-inducing antiepilepsy drugs (AEDs). The clearance of zonisamide is increased to 0.5 mL/min/kg in patients concurrently on enzyme-inducing AEDs.

Renal clearance is about 3.5 mL/min. The clearance of an oral dose of zonisamide from RBC is 2 mL/min.

## Special Populations

### Renal Insufficiency

Single 300 mg zonisamide doses were administered to three groups of volunteers. Group 1 was a healthy group with a creatinine clearance ranging from 70 to 152 mL/min. Group 2 and Group 3 had creatinine clearances ranging from 14.5 to 59 mL/min and 10 to 20 mL/min, respectively. Zonisamide renal clearance decreased with decreasing renal function (3.42, 2.50, 2.23 mL/min, respectively). Marked renal impairment (creatinine clearance < 20 mL/min) was associated with an increase in zonisamide AUC of 35% (see DOSAGE AND ADMINISTRATION section).

### Hepatic Disease

The pharmacokinetics of zonisamide in patients with impaired liver function have not been studied (see DOSAGE AND ADMINISTRATION section).

### Age

The pharmacokinetics of a 300 mg single dose of zonisamide was similar in young (mean age 28 years) and elderly subjects (mean age 69 years).

### Gender and Race

Information on the effect of gender and race on the pharmacokinetics of zonisamide is not available.

### Interactions of Zonisamide with Other Antiepilepsy Drugs (AEDs)

Concurrent medication with drugs that either induce or inhibit CYP3A4 may alter serum concentrations of zonisamide. Concomitant administration of phenytoin and carbamazepine increases zonisamide plasma clearance from 0.30 to 0.35 mL/min/kg to 0.35 to 0.5 mL/min/kg. The half-life of zonisamide is decreased to 27 hours by phenytoin, to 38 hours by phenobarbital and carbamazepine, and to 46 hours by valproate. Plasma protein binding of phenytoin and carbamazepine was not affected by zonisamide administration (see PRECAUTIONS: Drug Interactions subsection).

## Clinical Studies

The effectiveness of zonisamide as adjunctive therapy (added to other antiepilepsy drugs) has been established in three multicenter, placebo-controlled, double blind, 3-month clinical trials (two domestic, one European) in 499 patients with refractory partial onset seizures with or without secondary generalization. Each patient had a history of at least four partial onset seizures per month in spite of receiving one or two antiepilepsy drugs at therapeutic concentrations. The 499 patients (209 women, 290 men) ranged in age from 13 to 68 years with a mean age of about 35 years. In the two U.S. studies, over 80% of patients were Caucasian; 100% of patients in the European study were Caucasian. Zonisamide or placebo was added to the existing therapy. The primary measure of effectiveness was median percent reduction from baseline in partial seizure frequency. The secondary measure was proportion of patients achieving a 50% or greater seizure reduction from baseline (responders). The results described below are for all partial seizures in the intent-to-treat populations.

In the first study (n = 203), all patients had a 1-month baseline observation period, then received placebo or zonisamide in one of two dose escalation regimens; either 1) 100 mg/day for 5 weeks, 200 mg/day for one week, 300 mg/day for one week, and then 400 mg/day for 5 weeks; or 2) 100 mg/day for one week, followed by 200 mg/day for 5 weeks, then 300 mg/day for one week, then 400 mg/day for 5 weeks. This design allowed a 100 mg vs. placebo comparison over weeks 1 to 5, and a 200 mg vs. placebo comparison over weeks 2 to 6; the primary comparison was 400 mg (both escalation groups combined) vs. placebo over weeks 8 to 12. The total daily dose was given as twice a day dosing. Statistically significant treatment differences favoring zonisamide were seen for doses of 100, 200, and 400 mg/day.

In the second (n = 152) and third (n = 138) studies, patients had a 2 to 3 month baseline, then were randomly assigned to placebo or zonisamide for 3 months. Zonisamide was introduced by administering 100 mg/day for the first week, 200 mg/day the second week, then 400 mg/day for 2 weeks, after which the dose (zonisamide or placebo) could be adjusted as necessary to a maximum dose of 20 mg/kg/day or a maximum plasma level of 40 mcg/mL. In the second study, the total daily dose was given as twice a day dosing; in the third study, it was given as a single daily dose. The average final maintenance doses received in the studies were 530 and 430 mg/day in the second and third studies, respectively. Both studies demonstrated statistically significant differences favoring zonisamide for doses of 400 to 600 mg/day, and there was no apparent difference between once daily and twice daily dosing (in different studies). Analysis of the data (first 4 weeks) during titration demonstrated statistically significant differences favoring zonisamide at doses between 100 and 400 mg/day. The primary comparison in both trials was for any dose over Weeks 5 to 12.

Table 1. Median % Reduction in All Partial Seizures and % Responders in Primary Efficacy Analyses: Intent-To-Treat Analysis

Study	Median % reduction in partial seizures		% Responders	
	Zonisamide	Placebo	Zonisamide	Placebo
<b>Study 1:</b>	n = 98	n = 72	n = 98	n = 72
<b>Weeks 8 to 12:</b>	40.5% *	9%	41.8% *	22.2%
<b>Study 2:</b>	n = 69	n = 72	n = 69	n = 72
<b>Weeks 5 to 12:</b>	29.6% *	-3.2%	29%	15%
<b>Study 3:</b>	n = 67	n = 66	n = 67	n = 66
<b>Weeks 5 to 12</b>	27.2% *	-1.1%	28% *	12%

\*p&lt;0.05 compared to placebo

Table 2. Median % Reduction in All Partial Seizures and % Responders for Dose Analyses in Study 1: Intent-To-Treat Analysis

Dose Group	Median % reduction in partial seizures		% Responders	
	Zonisamide	Placebo	Zonisamide	Placebo
<b>100 to 400 mg/day:</b>	n = 112	n = 83	n = 112	n = 83
<b>Weeks 1 to 12:</b>	32.3% *	5.6%	32.1% *	9.6 %
<b>100 mg/day:</b>	n = 56	n = 80	n = 56	n = 80
<b>Weeks 1 to 5:</b>	24.7% *	8.3%	25% *	11.3%
<b>200 mg/day:</b>	n = 55	n = 82	n = 55	n = 82
<b>Weeks 2 to 6</b>	20.4% *	4%	25.5% *	9.8%

\*p&lt;0.05 compared to placebo

Figure 1 presents the proportion of patients (X-axis) whose percentage reduction from baseline in the all partial seizure rate was at least as great as that indicated on the Y-axis in the second and third placebo-controlled trials. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in seizure rate), while a negative value indicates a worsening from baseline (i.e., an increase in seizure rate). Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in seizure rate was consistently higher for the zonisamide groups compared to the placebo groups. For example, Figure 1 indicates that approximately 27% of patients treated with zonisamide experienced a 75% or greater reduction, compared to approximately 12% in the placebo groups.

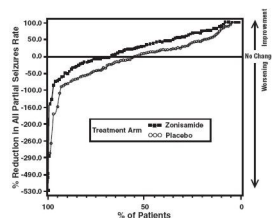


Figure 1 Proportion of Patients Achieving Differing Levels of Seizure Reduction in Zonisamide and Placebo Groups in Studies 2 and 3

No differences in efficacy based on age, sex or race, as measured by a change in seizure frequency from baseline, were detected.

## INDICATIONS AND USAGE

Zonisamide capsules are indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

## CONTRAINDICATIONS

Zonisamide capsules are contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

## WARNINGS

*Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson Syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide-type adverse reaction to zonisamide is described below.*

## **Serious Skin Reactions**

**Consideration should be given to discontinuing zonisamide in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently.** Seven deaths from severe rash [i.e. Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)] were reported in the first 11 years of marketing in Japan. All of the patients were receiving other drugs in addition to zonisamide. In post-marketing experience from Japan, a total of 49 cases of SJS or TEN have been reported, a reporting rate of 46 per million patient-years of exposure. Although this rate is greater than background, it is probably an underestimate of the true incidence because of under-reporting. There were no confirmed cases of SJS or TEN in the U.S., European, or Japanese development programs.

In the U.S. and European randomized controlled trials, 6 of 269 (2.2%) zonisamide patients discontinued treatment because of rash compared to none on placebo. Across all trials during the U.S. and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12 events per 1,000 patient-years of exposure). During Japanese development, serious rash or rash that led to study drug discontinuation was reported in 2% of patients (27.8 events per 1,000 patient years). Rash usually occurred early in treatment, with 85% reported within 16 weeks in the U.S. and European studies and 90% reported within 2 weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

## **Serious Hematologic Events**

Two confirmed cases of aplastic anemia and one confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan, rates greater than generally accepted background rates. There were no cases of aplastic anemia and two confirmed cases of agranulocytosis in the U.S., European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

## **Oligohidrosis and Hyperthermia in Pediatric Patients**

**Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.**

During the pre-approval development program in Japan, one case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases reported in the U.S. or European development programs, fewer than 100 pediatric patients participated in these trials.

In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case per 10,000 patient-years of exposure. In the first year of marketing in the U.S., 2 cases were reported, an estimated reporting rate of about 12 cases per 10,000 patient-years of exposure. These rates are underestimates of the true incidence because of under-reporting. There has also been one report of heat stroke in an 18-year-old patient in the U.S.

Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases. There have been no reported deaths.

Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with zonisamide should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when zonisamide is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, carbonic anhydrase inhibitors and drugs with anticholinergic activity.

The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.

## **Suicidal Behavior and Ideation**

Antiepileptic drugs (AEDs), including zonisamide, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing zonisamide or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers (see WARNINGS: Cognitive/Neuropsychiatric Adverse Events subsection below).

### Seizures on Withdrawal

As with other AEDs, abrupt withdrawal of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of zonisamide should be done gradually.

### Teratogenicity

Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of zonisamide during pregnancy in humans may present a significant risk to the fetus (see PRECAUTIONS: Pregnancy subsection). It cannot be said with any confidence, however, that even mild seizures do not pose some hazards to the developing fetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Cognitive/Neuropsychiatric Adverse Events

Use of zonisamide was frequently associated with central nervous system-related adverse events. The most significant of these can be classified into three general categories: 1) psychiatric symptoms, including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and 3) somnolence or fatigue. In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized for depression compared to 0.4% of placebo patients. Among all epilepsy patients treated with zonisamide, 1.4% were discontinued and 1% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued zonisamide or were hospitalized due to psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all epilepsy patients treated with zonisamide, 0.9% were discontinued and 1.4% were hospitalized because of reported psychosis or related symptoms.

Psychomotor slowing and difficulty with concentration occurred in the first month of treatment and were associated with doses above 300 mg/day. Speech and language problems tended to occur after 6 to 10 weeks of treatment and at doses above 300 mg/day. Although in most cases these events were of mild to moderate severity, they at times led to withdrawal from treatment.

Somnolence and fatigue were frequently reported CNS adverse events during clinical trials with zonisamide. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue tended to occur within the first month of treatment. Somnolence and fatigue occurred most frequently at doses of 300 to 500 mg/day. **Patients should be cautioned about this possibility and special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.**

### PRECAUTIONS

#### General

Somnolence is commonly reported, especially at higher doses of zonisamide (see WARNINGS: Cognitive/Neuropsychiatric Adverse Events subsection). Zonisamide is metabolized by the liver and eliminated by the kidneys; caution should therefore be exercised when

administering zonisamide to patients with hepatic and renal dysfunction (see CLINICAL PHARMACOLOGY: Special Populations subsection).

### **Kidney Stones**

Among 991 patients treated during the development of zonisamide, 40 patients (4%) with epilepsy receiving zonisamide developed clinically possible or confirmed kidney stones (e.g., clinical symptomatology, sonography, etc.), a rate of 34 per 1,000 patient-years of exposure (40 patients with 1,168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 28.7 per 1,000 patient-years of exposure in the first six months, 62.6 per 1,000 patient-years of exposure between 6 and 12 months, and 24.3 per 1,000 patient-years of exposure after 12 months of use. There are no normative sonographic data available for either the general population or patients with epilepsy. The clinical significance of the sonographic finding is unknown. The analyzed stones were composed of calcium or urate salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patients treated with zonisamide.

### **Effect on Renal Function**

In several clinical studies, zonisamide was associated with a statistically significant 8% mean increase from baseline of serum creatinine and blood urea nitrogen (BUN) compared to essentially no change in the placebo patients. The increase appeared to persist over time but was not progressive; this has been interpreted as an effect on glomerular filtration rate (GFR). There were no episodes of unexplained acute renal failure in clinical development in the U.S., Europe, or Japan. The decrease in GFR appeared within the first 4 weeks of treatment. In a 30-day study, the GFR returned to baseline within 2 to 3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effects on GFR after long-term use. Zonisamide should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration. Zonisamide should not be used in patients with renal failure (estimated GFR < 50 mL/min) as there has been insufficient experience concerning drug dosing and toxicity.

### **Sudden Unexplained Death in Epilepsy**

During the development of zonisamide, nine sudden unexplained deaths occurred among 991 patients with epilepsy receiving zonisamide for whom accurate exposure data are available. This represents an incidence of 7.7 deaths per 1,000 patient years. Although this rate exceeds that expected in a healthy population, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with refractory epilepsy not receiving zonisamide (ranging from 0.5 per 1,000 patient-years for the general population of patients with epilepsy, to 2 to 5 per 1,000 patient-years for patients with refractory epilepsy; higher incidences range from 9 to 15 per 1,000 patient-years among surgical candidates and surgical failures). Some of the deaths could represent seizure-related deaths in which the seizure was not observed.

### **Status Epilepticus**

Estimates of the incidence of treatment emergent status epilepticus in zonisamide-treated patients are difficult because a standard definition was not employed. Nonetheless, in controlled trials, 1.1% of patients treated with zonisamide had an event labeled as status epilepticus compared to none of the patients treated with placebo. Among patients treated with zonisamide across all epilepsy studies (controlled and uncontrolled), 1% of patients had an event reported as status epilepticus.

### **Information for Patients**

Patients should be informed of the availability of a Medication Guide, and they should be instructed to read the Medication Guide prior to taking zonisamide. Patients should be instructed to take zonisamide only as prescribed.

Patients should be advised as follows: (See Medication Guide)

1. **Zonisamide may produce drowsiness, especially at higher doses. Patients should be advised not to drive a car or operate other complex machinery until they have gained experience on zonisamide sufficient to determine whether it affects their performance.**
2. Patients should contact their physician immediately if a skin rash develops or seizures worsen.
3. Patients should contact their physician immediately if they develop signs or symptoms, such as sudden back pain, abdominal pain, and/or blood in the urine, that could indicate a kidney stone. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for stones.
4. Patients should contact their physician immediately if a child has been taking zonisamide and is not sweating as usual with or without a fever.
5. Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.

6. **Suicidal Thinking and Behavior:** Patients, their caregivers, and families should be counseled that AEDs, including zonisamide, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
7. As with other AEDs, patients should contact their physician if they intend to become pregnant or are pregnant during zonisamide therapy. Patients should notify their physician if they intend to breast-feed or are breast-feeding an infant.

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS: Pregnancy subsection).

8. Patients should contact their physician immediately if they develop severe muscle pain and/or weakness.

### Laboratory Tests

In several clinical studies, zonisamide was associated with a mean increase in the concentration of serum creatinine and blood urea nitrogen (BUN) of approximately 8% over the baseline measurement. Consideration should be given to monitoring renal function periodically (see PRECAUTIONS: Effect on Renal Function subsection).

Zonisamide was associated with an increase in serum alkaline phosphatase. In the randomized, controlled trials, a mean increase of approximately 7% over baseline was associated with zonisamide compared to a 3% mean increase in placebo-treated patients. These changes were not statistically significant. The clinical relevance of these changes is unknown.

### Drug Interactions

#### Effects of Zonisamide on the Pharmacokinetics of Other Antiepilepsy Drugs (AEDs)

Zonisamide had no appreciable effect on the steady-state plasma concentrations of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidase enzymes (cytochrome P450), as measured in human liver microsomal preparations, *in vitro*. Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by cytochrome P450 isozymes.

#### Effects of Other Drugs on Zonisamide Pharmacokinetics

Drugs that induce liver enzymes increase the metabolism and clearance of zonisamide and decrease its half-life. The half-life of zonisamide following a 400 mg dose in patients concurrently on enzyme-inducing AEDs such as phenytoin, carbamazepine, or phenobarbital was between 27 to 38 hours; the half-life of zonisamide in patients concurrently on the non-enzyme inducing AED, valproate, was 46 hours. Concurrent medication with drugs that either induce or inhibit CYP3A4 would be expected to alter serum concentrations of zonisamide.

#### Interaction with Cimetidine

Zonisamide single dose pharmacokinetic parameters were not affected by cimetidine (300 mg four times a day for 12 days).

### Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found in mice or rats following dietary administration of zonisamide for 2 years at doses of up to 80 mg/kg/day. In mice, this dose is approximately equivalent to the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m<sup>2</sup> basis. In rats, this dose is 1 to 2 times the MRHD on a mg/m<sup>2</sup> basis.

Zonisamide increased mutation frequency in Chinese hamster lung cells in the absence of metabolic activation. Zonisamide was not mutagenic or clastogenic in the Ames test, mouse lymphoma assay, sister chromatid exchange test, and human lymphocyte cytogenetics assay *in vitro*, and the rat bone marrow cytogenetics assay *in vivo*.

Rats treated with zonisamide (20, 60, or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m<sup>2</sup> basis. The effect of zonisamide on human fertility is unknown.

### Pregnancy

#### Teratogenic Effects

#### Pregnancy Category C

(see WARNINGS: Teratogenicity subsection)

Zonisamide was teratogenic in mice, rats, and dogs and embryo-lethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryo-fetal deaths occurred in these species at zonisamide dosage and maternal plasma

levels similar to or lower than therapeutic levels in humans, indicating that use of this drug in pregnancy entails a significant risk to the fetus. A variety of external, visceral, and skeletal malformations was produced in animals by prenatal exposure to zonisamide. Cardiovascular defects were prominent in both rats and dogs.

Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (25 mcg/mL) about 0.5 times the highest plasma levels measured in patients receiving the maximum recommended human dose (MRHD) of 400 mg/day. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with maternal plasma levels (44 mcg/mL) approximately equal to the highest levels measured in humans receiving the MRHD. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses in this study. The low dose produced maternal plasma levels (12 mcg/mL) about 0.25 times the highest human levels.

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryo-fetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryo-lethal dose in monkeys was associated with peak maternal plasma zonisamide levels (5 mcg/mL) approximately 0.1 times the highest levels measured in patients at the MRHD.

In a mouse embryo-fetal development study, treatment of pregnant animals with zonisamide (125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. The low dose in this study is approximately 1.5 times the MRHD on a  $\text{mg}/\text{m}^2$  basis. In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among the offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose is approximately 0.5 times the MRHD on a  $\text{mg}/\text{m}^2$  basis.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60 mg/kg/day) from the latter part of gestation up to weaning at the high dose, or approximately 1.4 times the MRHD on a  $\text{mg}/\text{m}^2$  basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the MRHD on a  $\text{mg}/\text{m}^2$  basis.

There are no adequate and well controlled studies in pregnant women. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To provide information regarding the effects of *in utero* exposure to zonisamide, physicians are advised to recommend that pregnant patients taking zonisamide enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

### **Labor and Delivery**

The effect of zonisamide on labor and delivery in humans is not known.

### **Use in Nursing Mothers**

It is not known whether zonisamide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from zonisamide, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother. Zonisamide should be used in nursing mothers only if the benefits outweigh the risks.

### **Pediatric Use**

The safety and effectiveness of zonisamide in children under age 16 have not been established. Cases of oligohydrosis and hyperpyrexia have been reported (see WARNINGS: Oligohydrosis and Hyperthermia in Pediatric Patients subsection).

### **Geriatric Use**

Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers (see CLINICAL PHARMACOLOGY: Special Populations subsection). Clinical studies of zonisamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.



## ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of zonisamide in controlled clinical trials that were not seen at an equivalent frequency among placebo-treated patients were somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability.

In controlled clinical trials, 12% of patients receiving zonisamide as adjunctive therapy discontinued due to an adverse event compared to 6% receiving placebo. Approximately 21% of the 1,336 patients with epilepsy who received zonisamide in clinical studies discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were somnolence, fatigue and/or ataxia (6%), anorexia (3%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse events were dose related (see WARNINGS and PRECAUTIONS).

### Adverse Event Incidence in Controlled Clinical Trials

Table 4 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with zonisamide in controlled clinical trials that were numerically more common in the zonisamide group. In these studies, either zonisamide or placebo was added to the patient's current AED therapy. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when zonisamide was added to concurrent AED therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Table 4. Incidence (%) of Treatment-Emergent Adverse Events in Placebo- Controlled, Add-On Trials (Events that occurred in at least 2% of zonisamide-treated patients and occurred more frequently in zonisamide-treated than placebo-treated patients)

BODY SYSTEM/PREFERRED TERM	ZONISAMIDE (n=269) %	PLACEBO (n=230) %
<b>BODY AS A WHOLE</b>		
Headache	10	8
Abdominal Pain	6	3
Flu Syndrome	4	3
<b>DIGESTIVE</b>		
Anorexia	13	6
Nausea	9	6
Diarrhea	5	2
Dyspepsia	3	1
Constipation	2	1
Dry Mouth	2	1
<b>HEMATOLOGIC AND LYMPHATIC</b>		
Ecchymosis	2	1
<b>METABOLIC AND NUTRITIONAL</b>		
Weight Loss	3	2
<b>NERVOUS SYSTEM</b>		
Dizziness	13	7
Ataxia	6	1
Nystagmus	4	2
Paresthesia	4	1
<b>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-ALTERED COGNITIVE FUNCTION</b>		
Confusion	6	3
Difficulty Concentrating	6	2
Difficulty with Memory	6	2
Mental Slowing	4	2
<b>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (NON-PSYCHOSIS RELATED)</b>		
Agitation/Irritability	9	4

Depression	6	3
Insomnia	6	3
Anxiety	3	2
Nervousness	2	1
<b>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (PSYCHOSIS RELATED)</b>		
Schizophrenic/Schizophreniform Behavior	2	0
<b>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-CNS DEPRESSION</b>		
Somnolence	17	7
Fatigue	8	6
Tiredness	7	5
<b>NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-SPEECH AND LANGUAGE ABNORMALITIES</b>		
Speech Abnormalities	5	2
Difficulties in Verbal Expression	2	< 1
<b>RESPIRATORY</b>		
Rhinitis	2	1
<b>SKIN AND APPENDAGES</b>		
Rash	3	2
<b>SPECIAL SENSES</b>		
Diplopia	6	3
Taste Perversion	2	0

#### Other Adverse Events Observed During Clinical Trials

Zonisamide has been administered to 1,598 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all events were recorded by the investigators using their own terms. To provide a useful estimate of the proportion of individuals having adverse events, similar events have been grouped into a smaller number of standardized categories using a modified COSTART dictionary. The frequencies represent the proportion of the 1,598 individuals exposed to zonisamide who experienced an event on at least one occasion. All events are included except those already listed in the previous table or discussed in WARNINGS or PRECAUTIONS, trivial events, those too general to be informative, and those not reasonably associated with zonisamide.

Events are further classified within each category and listed in order of decreasing frequency as follows: frequent occurring in at least 1:100 patient; infrequent occurring in 1:100 to 1:1,000 patients; rare occurring in fewer than 1:1,000 patients.

**Body as a Whole:** *Frequent:* Accidental injury, asthenia. *Infrequent:* Chest pain, flank pain, malaise, allergic reaction, face edema, neck rigidity. *Rare:* Lupus erythematosus.

**Cardiovascular:** *Infrequent:* Palpitation, tachycardia, vascular insufficiency, hypotension, hypertension, thrombophlebitis, syncope, bradycardia. *Rare:* Atrial fibrillation, heart failure, pulmonary embolus, ventricular extrasystoles.

**Digestive:** *Frequent:* Vomiting. *Infrequent:* Flatulence, gingivitis, gum hyperplasia, gastritis, gastroenteritis, stomatitis, cholelithiasis, glossitis, melena, rectal hemorrhage, ulcerative stomatitis, gastro-duodenal ulcer, dysphagia, gum hemorrhage. *Rare:* Cholangitis, hematemesis, cholecystitis, cholestatic jaundice, colitis, duodenitis, esophagitis, fecal incontinence, mouth ulceration.

**Hematologic and Lymphatic:** *Infrequent:* Leukopenia, anemia, immunodeficiency, lymphadenopathy. *Rare:* Thrombocytopenia, microcytic anemia, petechia.

**Metabolic and Nutritional:** *Infrequent:* Peripheral edema, weight gain, edema, thirst, dehydration. *Rare:* Hypoglycemia, hyponatremia, lactic dehydrogenase increased, SGOT increased, SGPT increased.

**Musculoskeletal:** *Infrequent:* Leg cramps, myalgia, myasthenia, arthralgia, arthritis.

**Nervous System:** *Frequent:* Tremor, convulsion, abnormal gait, hyperesthesia, incoordination. *Infrequent:* Hypertonia, twitching, abnormal dreams, vertigo, libido decreased, neuropathy, hyperkinesia, movement disorder, dysarthria, cerebrovascular accident, hypotonia, peripheral neuritis, parathesia, reflexes increased. *Rare:* Circumoral paresthesia, dyskinesia, dystonia, encephalopathy, facial paralysis, hypokinesia, hyperesthesia, myoclonus, oculogyric crisis.

**Behavioral Abnormalities-Non-Psychosis-Related:** *Infrequent:* Euphoria.

**Respiratory:** *Frequent:* Pharyngitis, cough increased. *Infrequent:* Dyspnea. *Rare:* Apnea, hemoptysis.

**Skin and Appendages:** *Frequent:* Pruritus. *Infrequent:* Maculopapular rash, acne, alopecia, dry skin, sweating, eczema, urticaria, hirsutism, pustular rash, vesiculobullous rash.

**Special Senses:** *Frequent:* Amblyopia, tinnitus. *Infrequent:* Conjunctivitis, parosmia, deafness, visual field defect, glaucoma. *Rare:* Photophobia, iritis.

**Urogenital:** *Infrequent:* Urinary frequency, dysuria, urinary incontinence, hematuria, impotence, urinary retention, urinary urgency, amenorrhea, polyuria, nocturia. *Rare:* Albuminuria, enuresis, bladder pain, bladder calculus, gynecomastia, mastitis, menorrhagia.

## **DRUG ABUSE AND DEPENDENCE**

The abuse and dependence potential of zonisamide has not been evaluated in human studies (see **WARNINGS: Cognitive/Neuropsychiatric Adverse Events** subsection). In a series of animal studies, zonisamide did not demonstrate abuse liability and dependence potential. Monkeys did not self-administer zonisamide in a standard reinforcing paradigm. Rats exposed to zonisamide did not exhibit signs of physical dependence of the CNS-depressant type. Rats did not generalize the effects of diazepam to zonisamide in a standard discrimination paradigm after training, suggesting that zonisamide does not have abuse potential of the benzodiazepine-CNS depressant type.

## **OVERDOSAGE**

### **Human Experience**

Experience with zonisamide daily doses over 800 mg/day is limited. During zonisamide clinical development, three patients ingested unknown amounts of zonisamide as suicide attempts, and all three were hospitalized with CNS symptoms. One patient became comatose and developed bradycardia, hypotension, and respiratory depression; the zonisamide plasma level was 100.1 mcg/mL measured 31 hours post-ingestion. Zonisamide plasma levels fell with a half-life of 57 hours, and the patient became alert 5 days later.

### **Management**

No specific antidotes for zonisamide overdosage are available. Following a suspected recent overdose, emesis should be induced or gastric lavage performed with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring of vital signs and close observation.

Zonisamide has a long half-life (see **CLINICAL PHARMACOLOGY** section). Due to the low protein binding of zonisamide (40%), renal dialysis may not be effective. The effectiveness of renal dialysis as a treatment of overdose has not been formally studied. A poison control center should be contacted for information on the management of zonisamide overdosage.

## **DOSAGE AND ADMINISTRATION**

Zonisamide capsules are recommended as adjunctive therapy for the treatment of partial seizures in adults. Safety and efficacy in pediatric patients below the age of 16 have not been established. Zonisamide capsules should be administered once or twice daily, using 25 mg, 50 mg or 100 mg capsules. Zonisamide capsules are given orally and can be taken with or without food. Capsules should be swallowed whole.

### **Adults Over Age 16**

The prescriber should be aware that, because of the long half-life of zonisamide, up to 2 weeks may be required to achieve steady-state levels upon reaching a stable dose or following dosage adjustment. Although the regimen described below is one that has been shown to be tolerated, the prescriber may wish to prolong the duration of treatment at the lower doses in order to fully assess the effects of zonisamide at steady-state, noting that many of the side effects of zonisamide are more frequent at doses of 300 mg per day and above. Although there is some evidence of greater response at doses above 100 to 200 mg/day, the increase appears small and formal dose-response studies have not been conducted.

The initial dose of zonisamide capsules should be 100 mg daily. After 2 weeks, the dose may be increased to 200 mg/day for at least 2 weeks. It can be increased to 300 mg/day and 400 mg/day, with the dose stable for at least 2 weeks to achieve steady-state at each level. Evidence from controlled trials suggests that zonisamide capsule doses of 100 to 600 mg/day are effective, but there is no suggestion of increasing response above 400 mg/day (see **CLINICAL PHARMACOLOGY: Clinical Studies** subsection). There is little experience with doses greater than 600 mg/day.

### **Patients with Renal or Hepatic Disease**

Because zonisamide is metabolized in the liver and excreted by the kidneys, patients with renal or hepatic disease should be treated with caution, and might require slower titration and more frequent monitoring (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

## **HOW SUPPLIED**

Zonisamide Capsules are available as 25 mg, 50 mg or 100 mg capsules.

The 25 mg capsule is a violet opaque cap/lavender opaque body, hard-shell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **6725** in black ink on both the cap and body. They are available as follows:

NDC 0378-6725-01

bottles of 100 capsules

NDC 0378-6725-05

bottles of 500 capsules

The 50 mg capsule is a violet opaque cap/white opaque body, hard-shell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **6726** in black ink on both the cap and body. They are available as follows:

NDC 0378-6726-01  
bottles of 100 capsules  
NDC 0378-6726-05  
bottles of 500 capsules

The 100 mg capsule is a violet opaque cap/light blue opaque body, hard-shell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **6727** in black ink on both the cap and body. They are available as follows:

NDC 0378-6727-01  
bottles of 100 capsules  
NDC 0378-6727-05  
bottles of 500 capsules

**Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]**

**Protect from moisture and light.**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

**PHARMACIST:** Dispense a Medication Guide with each prescription.

## **ANIMAL TOXICOLOGY**

In dogs treated with zonisamide (10, 30, or 75 mg/kg/day) for one year, dark brown discoloration of the liver and concentric lamellar bodies in the cytoplasm of hepatocytes were observed in association with clinical chemistry changes indicative of liver damage (elevated alkaline phosphatase, gamma glutamyl transferase, and alanine amino transferase; decreased albumin) and altered drug metabolism at the highest dose, which is approximately 6 times the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m<sup>2</sup> basis. Gross liver changes not clearly accompanied by biochemical evidence of hepatotoxicity were noted at 30 mg/kg/day, or approximately 2.4 times the MRHD on mg/m<sup>2</sup> basis. The no effect dose of 10 mg/kg/day is slightly less than the MRHD on mg/m<sup>2</sup> basis. The significance of these findings for humans is not known.

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505

REVISED OCTOBER 2009

ZONS:R2mpbmt

## **MEDICATION GUIDE ZONISAMIDE CAPSULES**

Read this Medication Guide before you start taking zonisamide capsules and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

### **What is the most important information I should know about zonisamide?**

1. Zonisamide may cause a serious skin rash that can cause death. These serious skin reactions are more likely to happen when you begin taking zonisamide within the first 4 months of treatment but may occur at later times.
2. Zonisamide may cause you to sweat less and to increase your body temperature (fever). You may need to be hospitalized for this. You should watch for decreased sweating and fever, especially when it is hot and especially in children taking zonisamide.

### **Call your healthcare provider right away if you have:**

- a skin rash
  - fever
  - less sweat than normal
3. **Zonisamide can cause blood cell abnormalities such as reduced red and white blood cell counts.** Call your healthcare provider if you develop fever, sore throat, sores in your mouth, or unusual bruising.
  4. **Like other antiepileptic drugs, zonisamide may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempt to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses

- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**Do not stop zonisamide without first talking to a healthcare provider.**

- Stopping zonisamide suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

**How can I watch for early symptoms of suicidal thoughts and actions?**

- Pay attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

**What is zonisamide?**

Zonisamide is a prescription medicine that is used with other medicines to treat partial seizures in adults.

It is not known if zonisamide is safe or effective in children under 16 years of age.

**Who should not take zonisamide?**

Do not take zonisamide if you are allergic to medicines that contain sulfa.

**What should I tell my healthcare provider before taking zonisamide?**

Before taking zonisamide, tell your healthcare provider about all your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior
- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. You and your healthcare provider will have to decide if you should take zonisamide while you are pregnant. If you become pregnant while taking zonisamide, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- are breast-feeding. It is not known if zonisamide passes into breast milk and if it can harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take zonisamide.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins or herbal supplements. Zonisamide and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist each time you get a new medicine.

**How should I take zonisamide?**

- Take zonisamide exactly as prescribed. Your healthcare prescriber may change your dose. Your healthcare provider will tell you how much zonisamide to take.
- Take zonisamide with or without food.
- Swallow the capsules whole.
- If you take too much zonisamide, call your local Poison Control Center or go to the nearest emergency room right away.
- Do not stop taking zonisamide without talking to your healthcare provider. Stopping zonisamide suddenly can cause serious problems, including seizures that will not stop (status epilepticus).
- Do not drive a car, work with machines, or do other dangerous activities until you know how zonisamide affects you. Zonisamide may make you drowsy.

**What are the possible side effects of zonisamide?**

Zonisamide can cause serious side effects including:

- The side effects mentioned above (see “What is the most important information I should know about zonisamide?”)
- **worsening seizures**

- **kidney stones** (sudden back pain, stomach pain, or blood in your urine)
- **problems with mood or thinking** (new or worse depression; sudden changes in mood, behavior, or loss of contact with reality, sometimes associated with hearing voices or seeing things that are not really there; feeling sleepy or tired; trouble concentrating; speech and language problems)

Call your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of zonisamide include:

- drowsiness
- loss of appetite
- dizziness
- trouble with walking and coordination
- headache
- nausea
- agitation
- irritability

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all of the possible side effects of zonisamide. For more information, ask your healthcare provider or pharmacist.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

**How should I store zonisamide?**

- Store zonisamide capsules at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
- Protect from moisture and light.
- **Keep zonisamide capsules and all medicines out of the reach of children.**

#### **General information about the safe and effective use of zonisamide**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use zonisamide for a condition for which it was not prescribed. Do not give zonisamide to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about zonisamide. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about zonisamide that is written for health professionals.

For more information, call Mylan Pharmaceuticals Inc. toll free at 1-877-446-3679 (1-877-4-INFO-RX).

#### **What are the ingredients in zonisamide capsules?**

Active ingredient: zonisamide

Inactive ingredients: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The empty gelatin capsule shells contain D&C Red No. 28, FD&C Blue No. 1, gelatin and titanium dioxide. In addition, the 100 mg empty gelatin capsule contains FD&C Red No. 3. The imprinting ink contains the following: black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505

OCTOBER 2009

MG:ZONS:R1

**PRINCIPAL DISPLAY PANEL - 25 mg**

**NDC 0378-6725-01**

**ZONISAMIDE**

**CAPSULES**

**25 mg**

**PHARMACIST: PLEASE DISPENSE WITH  
ATTACHED MEDICATION GUIDE.**

**100 CAPSULES (Rx only)**

Each capsule contains:  
Zonisamide . . . . . 25 mg  
Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.  
Keep container tightly closed.  
**Keep this and all medication  
out of the reach of children.**  
**Store at 20° to 25°C (68° to 77°F).**  
**[See USP Controlled Room  
Temperature.]**  
**Protect from moisture and light.**  
**Usual Dosage:** See accompanying  
prescribing information.  
**Mylan Pharmaceuticals Inc.**  
**Morgantown, WV 26505**  
**RM6725A1**



**PRINCIPAL DISPLAY PANEL - 50 mg**  
**NDC 0378-6726-01**  
**ZONISAMIDE**  
**CAPSULES**  
**50 mg**  
**PHARMACIST: PLEASE DISPENSE WITH**  
**ATTACHED MEDICATION GUIDE.**  
**100 CAPSULES (Rx only)**  
Each capsule contains:  
Zonisamide . . . . . 50 mg  
Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.  
Keep container tightly closed.  
**Keep this and all medication  
out of the reach of children.**  
**Store at 20° to 25°C (68° to 77°F).**  
**[See USP Controlled Room  
Temperature.]**  
**Protect from moisture and light.**  
**Usual Dosage:** See accompanying  
prescribing information.  
**Mylan Pharmaceuticals Inc.**  
**Morgantown, WV 26505**  
**RM6726A1**



## PRINCIPAL DISPLAY PANEL - 100 mg

NDC 0378-6727-01

### ZONISAMIDE CAPSULES

100 mg

**PHARMACIST: PLEASE DISPENSE WITH  
ATTACHED MEDICATION GUIDE.**

100 CAPSULES (Rx only)

Each capsule contains:

Zonisamide . . . . . 100 mg

Dispense in a tight, light-resistant  
container as defined in the USP  
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication  
out of the reach of children.**

Store at 20° to 25°C (68° to 77°F).

[See USP Controlled Room  
Temperature.]

**Protect from moisture and light.**

Usual Dosage: See accompanying  
prescribing information.

**Mylan Pharmaceuticals Inc.**

**Morgantown, WV 26505**

**RM6727A1**



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